UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/821,832	03/30/2001	Thomas Tuschl	0399.2008-002	6240

23628 7590 03/09/2009

WOLF GREENFIELD & SACKS, P.C.
600 ATLANTIC AVENUE
BOSTON, MA 02210-2206

EXAMINER	
WOLLENBERGER, LOUIS V	
ART UNIT	PAPER NUMBER
1635	
MAIL DATE	DELIVERY MODE
03/09/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/821,832	TUSCHL ET AL.	
	Examiner	Art Unit	
	Louis Wollenberger	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12/12/2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *76-78,81,86-88,91,108,110,112,115-120 and 124-177* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *76-78,81,86-88,91,108,110,112,115-120 and 124-177* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/7/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application/Amendment/Claims

Applicant's response filed 12/12/2008 to the Non-Final Office Action mailed 6/12/2008 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 6/12/2008 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 76–78, 81, 86–88, 91, 108, 110, 112, 115–120, and 124-177, filed 3/11/08, are pending and under consideration.

Non-Statutory Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 76–78, 81, 86–88, 91, 108, 110, 112, 115–120, and 124-177 remain provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 17, 20-23, 76, and 80-85 of copending Application No. 10/255,568. Although the conflicting claims are not identical, they are not patentably distinct from each other because the conflicting application claims a method of mediating RNA interference of an mRNA in a cell comprising introducing into the cell double stranded RNA of from about 21 to about 23 nucleotides in length, and embodiments thereof wherein the mRNA is mammalian cellular mRNA.

Therefore, one of ordinary skill in the art would conclude that the invention defined in the claims at issue is anticipated by, or would have been an obvious variation of, the invention defined in a claim in the conflicting application.

In an earlier Action, mailed 1/29/07, it was pointed out by the Examiner that:

1) MPEP §804, Section I, Part B.1 states in part that "If "provisional" ODP rejections in two applications are the only rejections remaining in those applications, the examiner should withdraw the ODP rejection in the earlier filed application thereby permitting that application to issue without need of a terminal disclaimer. A terminal disclaimer must be required in the later-filed application before the ODP rejection can be withdrawn and the application permitted to issue";

2) the conflicting applications are effectively filed on the same day. Thus, Application 10/255,568 is not a "later-filed" application;

3) a terminal disclaimer has not been required or voluntarily filed in conflicting application 10/255,568

4) the instant ODP rejection is not the only rejection remaining in the instant application; and that

5) the conflicting applications are not divisional applications of one another. The applications were not filed as the result of a restriction requirement in one or the other. The applications were voluntarily filed as separate applications. Thus, the prohibition against using the '568 Application as a reference against the instant application does not apply.

The instant rejection is proper therefor.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Response to Applicant Remarks

Applicant neither disputes the double patenting rejection nor files a terminal disclaimer.

***

Claims 76–78, 81, 86–88, 91, 108, 110, 112, 115–120, and 124-177 remain provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 30 and 34-55 of copending Application No. 11/142,866.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the conflicting application claims a method for chemically and enzymatically synthesizing nuclease resistant (i.e., stabilized) siRNAs of 19-25 nucleotides that mediate RNA

interference. Absent convincing evidence to the contrary, the methods claimed therein would result in the production of dsRNAs having 3' hydroxyls.

One of skill would recognize that the methods for making dsRNA claimed in '866 could be used to make the dsRNAs now claimed in the instant application. Therefore, one of ordinary skill in the art would conclude that the products defined in the claims at issue are anticipated by, or would have been obvious in view of the methods for making defined in the claims in the conflicting application.

MPEP §804, Section I, Part B.1 states in part that "If "provisional" ODP rejections in two applications are the only rejections remaining in those applications, the examiner should withdraw the ODP rejection in the earlier filed application thereby permitting that application to issue without need of a terminal disclaimer. A terminal disclaimer must be required in the later-filed application before the ODP rejection can be withdrawn and the application permitted to issue."

Application No. 11/142,866 is a later filed application. However, a terminal disclaimer has not been filed in conflicting application Application No. 11/142,866. Additionally, the instant ODP rejection is not the only rejection remaining in the instant application.

Therefore, the instant rejection is maintained.

***

Claims 76–78, 81, 86–88, 91, 108, 110, 112, 115–120, and 124-177 remain provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 48, 49, 51, 53-57, 60-64, 67-73, and 75-125 of copending Application No. 10/433,050.

Although the conflicting claims are not identical, they are not patentably distinct from each other because Application 10/433050 claims an isolated double stranded RNA molecule 19-23 nucleotides in length that mediates target-specific modifications of a mammalian gene.

Therefore, one of ordinary skill in the art would conclude that the invention defined in the claims at issue is anticipated by, or would have been an obvious variation of, the invention defined in a claim in the conflicting application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Response to Arguments

Applicant reiterates past arguments.

Accordingly, the Examiner restates the instant rejections are not the only rejections remaining in the application and are therefore maintained. The conflicting applications have at least one common assignee and one common inventor, as acknowledged by Applicant in the Remarks filed 3/1//08. The common inventor would appear to be under obligation of assignment to the common assignee in each case. Unjustified timewise extension of patent rights to the same or obvious variant of the same invention would be obtained by at least the common inventor/assignee.

Nevertheless, with regard to the '050 and '866 applications above, the Examiner acknowledges the instant application is the earlier filed application.

Claim Rejections - 35 USC § 112, first paragraph (new matter)

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 86-88, 91, 112, 115-120, 124, 126, 142-153, and 166-177 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

The instant claims use product-by-process language to define the claimed double stranded RNAs, stating the isolated RNA "is obtained from double-stranded RNA that has been cleaved into fragments of 21 to 23 nucleotides," or, in the more particular embodiments, into fragments of "21" or "23" nucleotides.

MPEP 2163, Section II, Part A, states in part there is a strong presumption that an adequate written description of the claimed invention is present in the specification as filed, *Wertheim*, 541 F.2d at 262, 191 USPQ at 96; however, with respect to newly added or amended claims, applicant should show support in the original disclosure for the new or amended claims. The purpose of the written description requirement is "to ensure that the inventor had possession, as of the filing date of the application relied on, of the specific subject matter later claimed by him." MPEP 2138.05, I.

In the instant case, adequate written description support is not found in the instant application for the genus of processes recited in the claims for obtaining dsRNAs of 21-23 nucleotides in length using any cleavage process as now claimed.

The process as written is generic to any chemical, enzymatic, or physical process for cleaving double stranded RNA to produce RNAi-active 21, 22, or 23 nucleotide long double stranded RNAs, having any number of different physical features resulting from any such process. Adequate written description support is not found in the instant application for all these processes. Rather, the instant specification and prior filed provisional application to which support is relied on, describe only one (1) process for obtaining RNAi-active double stranded RNA from any other dsRNA. Furthermore, this process, involving Drosophila cell lysate, is not described as a cleavage process, but as a combination, which produces a mixture of double stranded RNA molecules of approximately 21-23 nucleotides in length having RNAi activity. The specification simply states it involves processing dsRNA to produce 21-23 nt RNAs.

For example, the instant application describes a process whereby long dsRNA is combined with a soluble extract derived from Drosophila embryo, thereby producing a combination. The combination is maintained under conditions in which the dsRNA is processed to RNA of about 21 to about 23 nucleotides. The application further describes a gel purification method for isolating the dsRNA products of this combination. There is no disclosure of any other cleavage process to produce 21-23 nucleotide RNAs capable of mediating RNAi, and obviousness cannot be relied on for written description support. The record shows the instant technology was a newly emerging field, and the length and structural features of the instantly claimed dsRNAs are essential to their RNAi activity. There is no evidence of record to show one of skill would reasonably recognize the Drosophila cell lysate method was generally representative of any cleavage process for producing 21-23-mers from any dsRNA, and there is no language in the application as filed characterizing the Drosophila cell lysate system as a

cleavage process, or any statements informing one of skill that any other cleavage process could be substituted for the Drosophila cell lysate system to obtain the same products.

Thus, the application as filed does not teach that the Drosophila cell lysate system is a cleavage system or process, or that it is representative of any other cleavage process for producing RNAs of 21-23 nts in length that mediate RNAi. Accordingly, applicant has not demonstrated they were in possession of the entire genus of cleavage processes for producing dsRNAs of 21-23 nts in length, and there is no evidence to suggest Applicant appreciated at the time of filing the Drosophila lysate system was a cleavage system. It is stated only that the Drosophila in vitro system can also be used to obtain RNA of about 21 to about 23 nucleotides in length which mediates RNA interference of the mRNA of a particular gene. Moreover, the instant application does not even characterize the process as enzymatic, chemical, or physical. It simply describes the combination and the products obtained thereby.

There are no other enzymatic, chemical, or physical cleavage processes described. Moreover, there is no disclosure teaching that RNAi-active RNAs of 21-23 nts in length with one or more non-standard nucleotides or deoxyribonucleotides may be obtained by cleavage of any dsRNA using any process, much less incubation in Drosophila cell lysate. See, for example, claim 112. It is unclear how the Drosophila cell lysate system may be used to cleave chemically modified dsRNA into 21-23-mers, and there is certainly no evidence to show such a system, which is now known to involve enzymatic processes, may be used to dice long, chemically modified (and allegedly nuclease resistant) dsRNAs into short, RNAi active species. Clearly, this process has not been described in the application as filed, and post-filing amendments claiming such a process represent new matter.

Accordingly, one of skill would not recognize Applicant was in possession of the complete genus of RNAi-competent dsRNAs produced by all such processes at the time of filing as now claimed.

Therefore, the instant claims as a whole are rejected for lack of written description support.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 154-177 are rejected under 35 U.S.C. 102(b) as being anticipated by Manche et al. (1992) *Molecular and Cellular Biology* 12:5238–5248, as evidenced by Stratagene pBluescript II Phagemid Vectors Instruction Manual for Catalog # 212207, downloaded from the Stratagene, Inc. website on January 11, 2007 (copy enclosed), and a Basic Local Alignment Search Tool (BLAST) analysis, available through NCBI, of nucleic acid sequence "cccggtacccagcttttgttccc" completed on January 11, 2007 (results enclosed).

Upon further review, it is noted that in submitting new claims 154-177 on 3/11/2008, Applicant failed to point out with particularity in the manner required by 37 CFR 1.111(b) how new claims 154-177 may be patentable over Manche et al., when, in fact, new claims 154-177, continue to broadly embrace any dsRNA of 23 nucleotides in length that "has sequence

correspondence to an mRNA to mediate RNA interference." Just as Manche et al. was applied to previous claims in this application, Manche et al. remains pertinent to claims 154-177, newly added by amendment on 3/11/08, drawn to 23-nt dsRNAs.

While certain claims of 154-177 contain product-by-process language, there is no evidence the products produced by said process are structurally distinct from those disclosed by Manche et al. (MPEP 2113).

As explained in previous Actions, Manche et al. teach the production and isolation of a series of short, double stranded RNAs for use in a study of the interaction and activation of the interferon-induced protein kinase DAI. With regard to the instant claims, Manche et al. teach a 23-nucleotide double stranded RNA at page 5239 (see the *Hae* III fragment in Fig. 1; see also Materials and Methods, pp. 5239-40; and Characteristics of synthetic dsRNA, pp. 5240-1).

For example, at page 5240, Manche et al. state that "Duplexed RNAs of defined sizes were made by annealing a 358-nt transcript synthesized by T7 RNA polymerase with complementary transcripts of various lengths synthesized by T3 RNA polymerase (Fig. 1A). After digestion of the RNA tails and residual single-stranded RNA, the dsRNAs were purified by electrophoresis in nondenaturing polyacrylamide gels. When analyzed in denaturing conditions (Fig. 1B), the individual strands of the dsRNA molecules were slightly heterogeneous, with chain lengths a few nucleotides longer or shorter than the input single strands as a result of the trimming process. When examined in a nondenaturing gel, however,the dsRNAs migrated as discrete bands, with mobilities similar to those of dsDNA markers (see Fig. 5A, lanes 3 to 9). As expected, the duplexes were sensitive to digestion

with RNase III, a dsRNA-specific enzyme, but resistant to digestion by single-stranded specific nucleases except after denaturation (data not shown)."

Accordingly, the short dsRNAs are taught as being isolated and used systematically, in a substantially purified form to study their effect, if any, in a DAI kinase activation assay. Manche et al. teach that 23-mers only slightly activate DAI, whereas full activity was approached with 55- to 85-bp dsRNAs (page 5240 and Fig. 2, page 5241).

While Manche et al. do not specifically teach the sequence of the isolated short dsRNAs, nor provide any suggestion that the isolated short dsRNAs will or will not inhibit the expression of a mammalian gene, Manche et al. teach that the the plasmid pBSII KS+, from Stratagene, Inc., La Jolla, Calif. was used as the source of the short dsRNAs. More specifically, the dsRNAs were produced by restriction endonuclease digestion of the multiple cloning site region to produce templates for in vitro transcription. The transcribed products were then purified and annealed, and then digested with RNase to produce the dsRNAs used in the study (see materials and methods, pp. 5239-5240, and Fig. 1B).

The pBSII KS+ vector appears to correspond to the pBluescript II KS (+), described on page 4 of the Stratagene pBluescript II Phagemid Vectors Instruction Manual, available online from the Stratagene website (copy enclosed). Based on the multiple cloning site map, provided at page 4 of the Manual, it appears that the *Hae* III fragment of the vector consists of the sequence "cccggtacccagcttttgttccc." *Hae* III appears to cut just 5' of the *Kpn* I site at the "ggcc" palindrome.

A BLAST analysis of this sequence against the refseq_rna database shows that the sequence shares substantial "correspondence to" a number of rat, mouse, and human mRNAs,

including Homo sapiens methyltransferase 11 domain containing 1 (METT11D1), transcript variant 2, mRNA (see, for example, page 7 of 12 of the BLAST search results of record, previously supplied to Applicant in an earlier Action).

Accordingly, while Manche et al. is silent as to the RNA interference properties, if any, of the disclosed 23-nucleotide double stranded RNA, Manche et al. is considered to inherently disclose a 23-nucleotide dsRNA that "has sequence correspondence" and complementarity to a mammalian cellular mRNA, as required by the instant claims. Given that sequence correspondence and/or complementarity is an essential feature of interfering dsRNAs insofar as their ability to sequence-specifically inhibit gene expression and act as a guide for the RISC, it would appear that Manche et al. teach a dsRNA product that meets each of the structural limitations of the instant claims.

Though silent as to an inherent property, Manche et al. need not teach or recognize this inherent feature to anticipate the instant claims, since, as set forth in MPEP §2112, "There is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure *at the time of invention*, but only that the subject matter is in fact inherent in the prior art reference. *Schering Corp. v. Geneva Pharm. Inc.*, 339 F.3d 1373, 1377, 67 USPQ2d 1664, 1668 (Fed. Cir. 2003)."

And although the Manche et al. 23-mer does not appear to share 100% identity and/or sequence complementarity with a mammalian mRNA, a substantial portion of the 23-mer does match or is complementary to several mammalian mRNAs (see pages 3 and 4, for example). This finding, along with the teaching in the specification at page 3, lines 15-20, that, with regard to siRNAs used in the invention, "It is not necessary that there be perfect correspondence of the

sequences, but the correspondence must be sufficient to enable the RNA to direct RNAi cleavage of the target mRNA" is considered to be sufficient to indicate that there is a basis in fact to support the determination that the dsRNA disclosed by Manche et al. is inherently RNAi competent against at least one mammalian mRNA as shown in the BLAST analysis previously supplied to Applicant in an earlier Action (MPEP §2112, Section IV).

Accordingly, because the 23-nucleotide double stranded RNA disclosed by Manche et al. meets each the structural requirements of the instant claims, it would necessarily possess the biochemical properties recited in the claims. A compound and its properties are inseparable.

Therefore, Manche et al. anticipates the instant claims.

As a practical matter, the Patent Office is not equipped to manufacture products by the myriad of processes put before it and then obtain prior art products and make physical comparisons therewith." *In re Brown*, 459 F.2d 531, 535, 173 USPQ 685, 688 (CCPA 1972) (MPEP §2113).

> Where applicant claims a composition in terms of a function, property or characteristic and the composition of the prior art is the same as that of the claim but the function is not explicitly disclosed by the reference, the examiner may make a rejection under both 35 U.S.C. 102 and 103, expressed as a 102/103 rejection. "There is nothing inconsistent in concurrent rejections for obviousness under 35 U.S.C. 103 and for anticipation under 35 U.S.C. 102." *In re Best*, 562 F.2d 1252, 1255 n.4, 195 USPQ 430, 433 n.4 (CCPA 1977). This same rationale should also apply to product, apparatus, and process claims claimed in terms of function, property or characteristic. Therefore, a 35 U.S.C. 102/103 rejection is appropriate for these types of claims as well as for composition claims.

A REFERENCE TEACHING PRODUCT APPEARING TO BE SUBSTANTIALLY IDENTICAL IS MADE THE BASIS OF A REJECTION, AND THE EXAMINER PRESENTS EVIDENCE OR REASONING TENDING TO SHOW INHERENCY, THE BURDEN SHIFTS TO THE APPLICANT TO SHOW AN UNOBVIOUS DIFFERENCE

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 76–78, 81, 86–88, 91, 108, 110, 112, 115–120, and 124-177 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Crooke et al. (US Patent 6,107,094), as evidenced by Tuschl et al. (US 20040259247 A1) and Amarzguioui et al. (2003) *Nucleic Acids Res.* 31:589-595.

Tuschl et al. and Amarzguioui et al. are not relied on herein as prior art but only to show that a property is inherent (MPEP 2124 and 2131.01). See rejection below.

Crooke et al. taught double-stranded RNAs of 17 and 20 base-pairs in length for purifying and characterizing mammalian dsRNAses (cols. 46-58). Exemplary embodiments are set forth in Table 1, column 51. The double stranded RNAs used for such purposes comprise sense and antisense strands, wherein the antisense strand is 100% complementary to a mammalian mRNA such as Ha-Ras. The antisense strand is generally chemically modified such that an 8-9 ribonucleotide gap or core is flanked by one or more 2'-sugar modified and/or phosphorothioate modified nucleotides. See column 50, Example 27-a; column 52, lines 40-55; column 4, lines 15-30; columns 5-6; column 7, lines 20-30; column 11; and column 14, for example. Oligoribonucleotides modified in this manner are generally referred to therein as gapmers or chimeras.

It is said that the oligoribonucleotide gapmers, and i.e., impliedly, dsRNase substrates comprising said gapmers (i.e., dsRNAs), may be from about 5 to about 50 nucleotides in length, or, more preferably, from about 15 to about 25 nucleoside subunits in length (col. 14, lines 10-20).

At column 8, lines 1-3, Crooke et al. expressly taught that part of their invention included useful substrates for dsRNases as well as affinity matrices comprising said substrates. In several working examples at columns 50-58, Crooke et al. taught that useful substrates for characterizing and purifying dsRNAes are dsRNAs of at least 17 and 20 base-pairs in length. In one method, it is taught the RNA affinity columns comprising said dsRNAs may be used to further purify dsRNases (column 53 and 55-58). Following purification, the dsRNase(s) may then be assayed using a double stranded RNA digestion assay, wherein dsRNA duplexes are incubated in an appropriate buffer containing the dsRNase(s). It is implied that various dsRNAs of various

lengths in the recommended range (15-25 and 5 to 50) and with various flanking chemical modifications could be used in such an assay for characterizing dsRNase activity from almost any mammalian cell type.

At figure 4, Crooke et al. show dsRNase cleavage products may further be isolated and characterized in terms of their relative lengths to determine where and if cleavage has occurred in any given dsRNA duplex. See also figures 7 and 8 and Example 28-b, showing similar analyses.

Crooke et al. do not explicitly teach dsRNA gapmers of 21, 22, or 23 nucleotides in length.

However, in view of the disclosure cited above, stating that a preferred length for such substrates is 15-25 nucleotides in length or, more broadly, 5 to 50 nucleotides in length, teaching that dsRNA gapmers may be used to purify and characterize dsRNase activities from mammalian cells, and showing that 17- and 20-nucleotide dsRNAs may be used for such purposes, it would have been obvious to one of skill that dsRNAs of 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, and 25 nucleotides in length could each be used for the same purposes. That is, on the basis of the Crooke et al. disclosure, one of skill would have immediately envisioned chemically and non-chemically modified dsRNAs of 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, and 25 nucleotides in length complementary to a mammalian gene (see Fig. 1, for example, showing an exemplary list of potential substrates). One of skill would have also reasonably predicted that each such substrate could be used in the applications exemplified therein for purifying and characterizing dsRNases. One of skill would have had reason to synthesize and use each dsRNase substrate of 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, and 25 in length because Crooke et al. teach that dsRNAs

of this length are substrates for dsRNase-catalyzed cleavage, and it would have been the normal desire of the scientist to further explore, expand upon, and understand the activities of mammalian dsRNases as taught by Crooke et al. One of skill would have further recognized that information gleaned from such studies would incidentally have been useful towards the optimization of the RNA gapmer method disclosed therein for targeted degradation of an mRNA via endogenous dsRNase activity, triggered by the introduction of an RNA gapmer, as taught by Crooke et al. (cols. 9-12, for example).

While Crooke et al. explicitly and implicitly taught the synthesis and use of dsRNAs (i.e., dsRNase substrates) of 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, and 25 in length and complementary to a mammalian gene for the purification and characterization of dsRNases from mammalian cells, Crooke et al. do not teach the isolation of dsRNAs of 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, and 25 in length obtained by cleavage of a dsRNA. However, Crooke et al. do teach dsRNA digestion assays (col. 54, for example, but see 48-58) and the isolation of the digestion products by polyacrylamide gel electrophoresis (Figs. 4-8, for example; see also cols. 48-58). It is clear that if a dsRNA substrate of 25 to about 50 nucleotides in length were used in such an assay (50-nt substrates are implicitly suggested by the disclosure at column 14, lines 8-20, suggesting that 50-bp RNA-RNA duplexes are recognized by dsRNases), the resulting cleavage products would likely be on the order of 10-25 nucleotides in length, as evidenced by the cleavage mechanism shown in Fig. 4 Accordingly, one of skill practicing this assay with substrates in the range of 25 to 50-nts in length would necessarily isolate dsRNA cleavage products of between 21 and 23 nucleotides in length, meeting the limitations of the instant produc-by-process claims. For example, see claims 86-88, 91, and 142, as well as others.

While Crooke et al. do not teach that the dsRNAs intended for use as substrates for dsRNases, mediate RNA interference of a mammalian gene, Crooke et al. clearly taught that the single stranded RNA gapmers disclosed therein do mediate mRNA cleavage in a sequence specific manner, when introduced into a cell, via the formation of an RNA-RNA duplex. The disclosure teaches that this duplex is recognized by an endogenous dsRNase that then cleaves the duplex in the region of sequence complementarity. See Fig. 4., for example, but see entire disclosure.

Therefore, in view of such disclosure, and in view of the evidence in the art teaching that short interfering dsRNAs may be chemically modified at the 3' and/or 5' ends with one or more 2'-sugar or phosphorothioate modifications (see Tuschl et al., US 20040259247 A1, paragraphs 14-16), and in view of instant claims 110 and 112, for example, stating that the claimed double stranded RNA may comprise one or more non-standard nucleotides, there is sufficient reason to believe the dsRNase substrates of 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, and 25 nucleotides in length and longer up to and including 50 nucleotides in length, taught by Crooke et al. would mediate RNAi of the gene to which they are targeted. As further evidenced by Tuschl et al., blunt-ended dsRNAs are RNAi-active (paragraph 9). As further evidenced by Amarzguioui et end-modified dsRNAs have RNAi activity. See Fig. 3 therein.

Thus, the product dsRNAs taught and suggested by Crooke et al. necessarily would mediate RNAi. Accordingly, because Crooke et al. disclosed products that are identical to those now claimed, Crooke et al. necessarily disclosed each of the biophysical and biochemical properties inherent to those products, including the RNAi properties recited in the instant claims (MPEP 2112 and 2145.II).

Where, as here, the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product. See In re Ludtke 441 F.2d 660, 169 USPQ 563 (CCPA 1971). Whether the rejection is based on "inherency" under 35 USC 102, or "prima facie obviousness" under 35 USC 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products. In re Best, Bolton, and Shaw, 195 USPQ 430, 433 (CCPA 1977) citing In re Brown, 59 CCPA 1036, 459 F.2d 531, 173 USPQ 685 (1972).

As Applicant knows, under the doctrine of inherency there is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure *at the time of invention*, but only that the subject matter is in fact inherent in the prior art reference. *Schering Corp. v. Geneva Pharm. Inc.*, 339 F.3d 1373, 1377, 67 USPQ2d 1664, 1668 (Fed. Cir. 2003).

Accordingly, in the absent of convincing evidence to the contrary, the instantly claimed invention would have been *prima facie* obvious to one of skill in the art at the time the invention was made.

Response to Arguments/Declaration under 37 CFR §1.132

Applicant's arguments filed 12/12/2008 traversing the instant rejection have been fully considered. The Declaration under 37 CFR 1.132 filed 12/12/2008 and accompanying the Remarks has also been fully considered but is insufficient to overcome the instant rejection of the claims based upon the instantly cited references, above.

With regard to the Declaration, the statements therein are directed to the use of the instantly claimed 21-23 nucleotide double stranded RNAs for mediating RNAi in a mammalian cell. While the use of double stranded 21-23 nt RNAs for inhibiting the expression of mammalian genes in mammalian cells may well have been novel and unobvious at the time of invention, the instant claims are drawn to products not methods, and are limited in scope by such function only to the extent the products embraced by the claims be capable of mediating RNAi. As the double stranded RNAs suggested by Crooke et al. meet all the structural requirements of the claims, the RNAs would necessarily have each of the properties associated with such molecules, including those properties recited in the claims. While the RNAi properties of the 21-23 mers may be unexpected and unknown to Crooke et al., these properties are, nevertheless, inherent to the molecules suggested by Crooke et al. Mere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention. *In re Wiseman*, 596 F.2d 1019, 201 USPQ 658 (CCPA 1979). Applicant presents no evidence any of the double-stranded molecules suggested or explicitly exemplified would not be capable of directing cleavage of a mammalian mRNA in any cell. In this regard, the instant claims do not require the dsRNAs be capable of mediating RNAi of a mammalian mRNA in a mammalian cell, but require only the ability to mediate RNAi of a mammalian gene.

Moreover, there is no evidence to suggest the surprising properties asserted by Applicant to be associated with 21-23 mers are not also associated with the 17 or 20 mers explicitly disclosed by Crooke et al. or, for that matter, with any of the other chemically modified 15-25 nt dsRNAs suggested by Crooke et al. That is, there is no evidence the surprising properties begin

and end with the 21-23 nt range specifically claimed and do not extend throughout the entire or nearly the entire range suggested by Crooke et al.

The Examiner agrees Crooke et al. do not teach or suggest that dsRNAs themselves may be used to mediate RNAi; however, Crooke et al. suggested the claimed method for producing dsRNA with each of the recited features. As a compound and its properties are inseparable, the dsRNAs suggested by the prior art would necessarily have the properties associated with such compounds, including those discovered by Applicant. The claims do not currently require steps for silencing gene expression, but merely require the compound so produced be one that would mediate RNAi. There is no evidence the compounds suggested by Crooke et al. do not mediate RNAi.

Applicant also argues the disclosures of Crooke are directed to single stranded antisense molecules. The Examiner agrees in part. While the Crooke et al. patent is primarily concerned with making and using single stranded antisense oligoribonucleotides, they also discuss the use of artificial substrates—short, double stranded, chemically modified RNAs, composed of two strands of equal length—for purifying and assaying endogenously produced dsRNases. It is reasonable to conclude Crooke et al. considers these substrates to be representative of, or models for, the double stranded structures formed in vivo when an antisense oligoribonucleotide of 15 to 25 nucleotides in length is introduced into a cell. As each reference is relevant for all it discloses and for all it would suggest to one of skill in the art at the time, one of skill would reasonably expect any dsRNA substrate of 15 to 25 bases pairs in length may be used for the same purpose to isolate and study dsRNases, particularly when Crooke et al. exemplify two substrates, 17 and 20 nt in length, that fairly represent midpoints in the size range recommended for single stranded

antisense oligonucleotides. While Crooke et al. do not specifically point to 21 to 23 mers, they do suggest the entire range of structures from 15 to 25, as specifically exemplified by two embodiments in this range of 17 and 20 bp each. Thus, it is reasonable to believe one of skill would readily envision each of the other possible substrates, comprising chemically modified RNAs of equal length, in the preferred range from 15-25 bp, including those formed from strands of 21, 22, 23, 24, and 25 nucleotides in length. They would be viewed as equivalents, having similar structures and similar properties to those (17 and 20 nts) specifically exemplified, differing from the 20-bp example by only 1, 2, 3, 4, and 5 nucleotides. Certainly, Crooke et al. do no teach away from any of these other possible embodiments.

A *prima facie* case of obviousness may be made when chemical compounds have very close structural similarities and similar utilities. "An obviousness rejection based on similarity in chemical structure and function entails the motivation of one skilled in the art to make a claimed compound, in the expectation that compounds similar in structure will have similar properties." *In re Payne*, 606 F.2d 303, 313, 203 USPQ 245, 254 (CCPA 1979). In the instant case there is no evidence any of these other embodiments would not also be suitable for the same purposes described by Crooke et al. Additionally, there is no evidence these other embodiments would not also be inherently capable of mediating RNA interference of the gene to which they are comlementary: Ha-Ras. As the dsRNAs disclosed by Crooke et al. meet the structural requirements of the claims, there is sufficient reason to believe they have the functional properties recited by the claims.

As explained in the rejection, Crooke et al. (US Patent 6,107,094) also describe the synthesis and use of double stranded, chemically modified short RNA molecules for the purpose

of purifying and characterizing RNase III enzymes from various organisms. While it is clear Crooke et al. (US Patent 6,107,094) do not teach using short dsRNA molecules to mediate RNAi, the instant claims do not require a step for mediating RNAi or silencing gene expression. The claims merely require the dsRNAs produced by the method have the ability to mediate RNAi. Applicant presents no evidence any of the dsRNAs in the range 15 to 25 bp in length suggested by Crooke et al. would not mediate RNAi.

Further, it is respectfully submitted that Crooke et al. do not need to suggest the entire range of 21-23 nts in length or specifically point to 21, 22, or 23-mers to anticipate or reasonably suggest the 21-23 mers specifically recited in the claims. Crooke et al. explicitly exemplified embodiments of 17 and 20 nts in length as examples of artificial substrates representative of double stranded structures formed in vivo when 15-25 nucleotide antisense oligoribonucleotides are introduced into cells in vivo. Whole number values being the only possible increments, one of skill might reasonably infer that, at the very least, a 21- or 22-bp embodiment, in the range generally preferred for antisense oligonucleotides (e.g., 15-25), as disclosed by Crooke et al., would also be suitable for the same purpose: purifying and assaying endogenous dsRNases. Crooke et al. does not teach away from any such expectation, and there is no reason to suspect one of skill would not reasonably expect the 15, 16, 18, 19, 21, 22, 23, 24, and 25-bp embodiments would function any differently from the 17 and 20-bp embodiments exemplified in the disclosure. Thus, one of skill would immediately have envisioned each of the possible substrates of 15-25-bp disclosed by Crooke et al., and reasonably expected each would have substantially the same properties and be useful for the same purposes. Accordingly, one of skill would have had reason to make and use any double stranded 15-25-bp RNA in the manner and

for the purposes taught by Crooke et al., since each would have been considered to be equivalent. The instant RNAs are embraced by this range, which is so small and so well defined as to be an express disclosure of each 21, 22, and 23-bp molecule. For example, it has been held that a prior art genus containing only 20 compounds and a limited number of variations in the generic chemical formula inherently anticipated a claimed species within the genus because "one skilled in [the] art would... envisage *each member*" of the genus. *In re Petering*, 301 F.2d 676, 681, 133 USPQ 275, 280 (CCPA 1962). Thus, hindsight reasoning is not necessary to arrive at the claimed invention, since the claimed invention is necessarily fully described by the genus disclosed.

Applicant also argues the reasoning in the rejection applied to those claims requiring the double stranded RNA be obtained from double stranded RNA that has been cleaved into fragments, stating the fact that a result may occur is insufficient to support a rejection based on inherency. The Examiner agrees with Applicant in principle, but respectfully points out the instant claims embrace cleavage by any method, including but not limited to enzymatic processing. Thus, even conceding Applicant's arguments as persuasive, the patentability of the instant claims is based on the product and does not depend on the process used to produce the product, unless it can be shown the process used to derive the product results in a structure that is patentably distinguishable from that disclosed in the prior art (MPEP 2113). Currently, there is no evidence to show the dsRNAs produced by the method recited in the claims have any characteristics distinct from those disclosed by Crooke et al. Once the examiner provides a rationale tending to show that the claimed product appears to be the same or similar to that of the prior art, although produced by a different process, the burden shifts to applicant to come

forward with evidence establishing an unobvious difference between the claimed product and the prior art product. *In re Marosi,* 710 F.2d 798, 802, 218 USPQ 289, 292 (Fed. Cir. 1983)

The instant claims are entirely generic as to the means used to cleave dsRNA to form 21-23 mers; thus, the claims embrace any means, chemical, enzymatic, or physical. Accordingly, a number of different dsRNAs, including blunt-ended RNAs are reasonably embraced by the claims.

However, were Applicant to amend the claims to require a particular form of cleavage, which was shown to impart structural characteristics distinct from those disclosed or suggested by Crooke et al., the rejection as applied to these claims would be withdrawn. As applicant knows, all amendments must be fully supported by the application as filed in the manner required by 35 USC 112. Particular attention is drawn to claim 112 and the like, which require the isolated dsRNA be obtained by cleavage of dsRNA and contain non-standard or deoxyribonucleotides. It is noted the dsRNAs disclosed by Crooke et al. are chemically modified and blunt ended. The instant claims embrace and currently do not exclude such structures.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Louis Wollenberger whose telephone number is (571)272-8144. The examiner can normally be reached on M-F, 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz can be reached on (571)272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Louis Wollenberger/
Examiner, Art Unit 1635
February 28, 2009

/JD Schultz/
Supervisory Patent Examiner, Art Unit 1635